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Lack of Association Between Adrenergic Receptor Genotypes and Survival in Heart Failure Patients Treated With Carvedilol or Metoprolol

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Objectives This study investigated the role of adrenergic receptor genetics on transplant-free survival in heart failure (HF).

Background Discordant results exist for genetic associations between adrenergic receptor alleles and end points of β-blocker response in HF patients.

Methods We identified 637 patients enrolled in 2 U.S. cardiovascular genetic registries with HF and left ventricular systolic dysfunction who were discharged on β-blocker, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), and diuretic medications. End points were determined through the national Social Security Death Master File and transplant records. We genotyped 5 polymorphisms in 3 genes: *ADRB1* (S49G, R389G), *ADRB2* (G16R, Q27E), and *ADRA2C* (Del322-325) using 5′ nuclease assays and performed a multivariable clinical-genetic analysis.

Results A total of 190 events (29.8%) occurred over a median follow-up of 1,070 days. Multivariable analysis showed a significant effect of 4 clinical factors on survival: age ($p = 0.006$), gender ($p = 0.005$), ejection fraction ($p = 0.0002$), and hemoglobin ($p = 0.00010$). There was no significant effect of the polymorphisms or haplotypes analyzed on survival.

Conclusions Genotypes and haplotypes of *ADRB1, ADRB2,* and *ADRA2C* did not significantly affect survival in metoprolol-treated or carvedilol-treated HF patients in this study. These results complement the findings of 2 similarly designed previous studies, but do not replicate an association of *ADRB2* haplotypes and survival. All 3 studies differ from a survival benefit reported for bucindolol-treated homozygous *ADRB1* R389 individuals. This may be attributable to a drug-specific interaction between genotype and outcome with bucindolol that does not seem to occur with metoprolol or carvedilol. (J Am Coll Cardiol 2008;52:644–51) © 2008 by the American College of Cardiology Foundation

Heart failure (HF) affects 5 million Americans and represents a major health care challenge, with 500,000 new cases and 250,000 deaths each year (1). Heart failure may arise from ischemic or nonischemic injury, and the natural history can differ widely among individuals, even those with similar cardiomyopathic states (2,3). Identifying responders and nonresponders to HF therapies could lead to improved quality of care and better allocation of medical resources (4,5).

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Central to the development, progression, and mode of treatment in HF is the adrenergic system, which is modulated through a family of pre-synaptic and post-synaptic α- and β-adrenergic receptors (ARs) (6,7). In particular, presynaptic α_{2C}-ARs (responsible for norepinephrine release) and cardiomyocyte β_1- and β_2-AR (the targets for norepinephrine and β-blockers) form a "circuit" that may initially promote maintenance of cardiac output, but ultimately act

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to accelerate progression of failure (8). These phenomena have been extensively studied and are shown to play an important role in the pathophysiology and progression of HF. As a result, treatment of HF patients with β-blockers has become a standard of care, which in the U.S. consists primarily of the use of 2 drugs, metoprolol succinate and carvedilol (9,10). Both metoprolol and carvedilol block β_1-AR as well as display other unique and drug-specific properties. Given the existence of genetic polymorphisms in the adrenergic receptor genes encoding α_{2C}-AR, β_1-AR, and β_2-AR (*ADRA2C, ADRB1, ADRB2*, respectively), the critical question has been raised as to whether genetic variations explain differences in individual β-blocker therapeutic response (11,12).

Over the past 10 years, several studies have shown that single-nucleotide polymorphisms (SNPs) in the *ADRB1, ADRB2,* and *ADRA2C* genes influence receptor function in vitro and in vivo (6,7). For example, the arginine residue at position 389 of the β_1-AR gene (*ADRB1* R389) alters the receptor-Gs interaction and acts as a gain-of-function polymorphism (13). This interesting result subsequently triggered a series of investigations into *ADRB1* and other SNPs in HF patients to assess the potential relationship between patient genotype and response to therapy. Several of these studies report significantly different responses based on genotype for end points such as exercise capacity, initial tolerability during β-blocker titration, changes in left ventricular ejection fraction (LVEF), and changes in left ventricular (LV) remodeling in response to β-blocker therapy (14–19). To date, not all of the reported associations have been independently replicated, making it difficult to draw definitive conclusions for clinical use (11,12,20). For the more clinically relevant outcome of survival in HF patients, the results are also mixed, although 2 recent reports are notable. One study shows unfavorable survival outcomes for clinically treated HF patients with a homozygous haplotype in the *ADRB2* gene, 16/27 RQ (21). Another study from the BEST (β-blocker Evaluation of Survival Trial) shows significantly reduced mortality in bucindolol- versus placebo-treated HF patients who are *ADRB1* R389 homozygotes (16). To test the hypothesis that adrenergic receptor genotypes affect the critical end point of survival in β-blocker–treated HF patients, we performed a large, dual-center study with comprehensive genotyping and analysis of SNPs in the *ADRB1*, *ADRB2*, and *ADRA2C* genes and haplotypes in *ADRB1* and *ADRB2*.

Methods

Study population. The starting population for this study was identified within cardiac catheterization laboratory-based genetic registries at the Duke University Medical Center, CATHGEN (22), and the Utah-based Registry of the Intermountain Heart Collaborative Study (23). Registry sizes at the time of database search were 5,172 for CATHGEN and 14,085 for Registry of the Intermountain Heart Collaborative Study. Blood samples for genetic storage were obtained at the time of cardiac catheterization. Clinical data were obtained through a combination of registry database queries as well as manual chart abstraction of medication records and defined clinical data fields.

Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
AR = adrenergic receptor
ARB = angiotensin II receptor blocker
CI = confidence interval
EF = ejection fraction
HF = heart failure
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
SNP = single-nucleotide polymorphism

These studies were conducted in compliance with human studies committees at Duke University and Intermountain Healthcare. Written informed consent was obtained from the study subjects at each institution for participation in their cardiovascular genetics registries. The institutional committee on human research at Duke University and Intermountain Healthcare also approved the current study protocol as performed.

We initially searched the 2 registry databases for patients with clinical diagnosis of HF and/or LV systolic dysfunction with ejection fraction (EF) ≤40% at the time of catheterization. Of the 1,405 patients identified, we subsequently excluded 768 subjects for 1 or more of the following reasons based on pre-defined study criteria: patient not discharged on standard HF medications including β-blocker (metoprolol succinate or carvedilol), angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), and/or loop diuretic; undocumented EF or EF >40% (diastolic HF); fewer than 30 days elapsed between most recent myocardial infarction and cardiac catheterization; serum creatinine >2.0 mg/dl; valve or congenital heart disease as primary cause of LV dysfunction; severe, life-threatening noncardiac comorbidities; or inadequate deoxyribonucleic acid (DNA) sample for genotyping. For patients with undocumented New York Heart Association (NYHA) functional class, we required treatment with a loop diuretic as evidence of clinically symptomatic HF (shortness of breath, fluid accumulation). Baseline LVEF ≤40% was required for inclusion, which for the majority of patients was determined by ventriculogram on the date of catheterization or by echocardiogram within 6 months of catheterization. For some patients, the method for determining EF was not documented in the chart. Ischemic or nonischemic HF etiology was assigned using results of coronary angiography and information in the medical record. Patients were classified as ischemic HF if they showed ≥70% diameter stenosis in at least 1 major coronary artery, or had a prior history of myocardial infarction or coronary revascularization. Within the nonischemic population, we also identified

a "clean coronary" subgroup using the categorical cutoff points at each institution for minimal coronary artery stenosis (≤25% stenosis, Duke; and <10% stenosis, Registry of the Intermountain Heart Collaborative Study).

Definition of study period and end point determination. The period of study for all patients was indexed from the date of cardiac catheterization (T0; range January 17, 1998, to June 26, 2006) through the date of end point determination (March 1, 2007) or until date of death or heart transplantation, whichever came first. End point determination was made through search of the Social Security Death Master File (24) and search of cardiac transplant records at each institution. Outcome data were kept at each institution and separate from genotyping and clinical data until the time of statistical analysis.

Genetic analysis (genotyping). Genomic DNA was isolated from whole blood using a commercially available kit (PureGene, Gentra Systems, Minneapolis, Minnesota) and diluted to a concentration of 4 ng/μl; 12 ng was used in each assay. The genotypes were determined by polymerase chain reaction using 5′ nuclease genotyping assays (Applied Biosystems, Foster City, California). For ADRB1 S49 and R389, Assays on Demand were used (Assay numbers C_8898508_10 and C_8898494_10). For ADRB2 G16 and Q27, Assays-by-Design were created using the primer and probe sequences listed in the Online Appendix. The amino acid position 322 insertion/deletion variant in the *ADRA2C* gene was less amenable to the genotyping platform, so we utilized a surrogate marker, which is an SNP that is in high linkage disequilibrium ($r^2 = 0.924$) to the deletion as described by Small et al. (25) (SNP "H"). Primer and probe sequences for this assay are also shown in the Online Appendix. For purposes of presentation, these results are shown as the insertion/deletion polymorphism at position 322 because this variation has been shown to affect receptor function.

Statistical methods. CLINICAL ANALYSIS. To assess the association of clinical characteristics with study end points, a series of univariate proportional hazards regression models were fit, 1 model for each of 12 pre-defined clinical factors. We prospectively defined a significance level of $p < 0.10$ for inclusion of clinical factors in the multivariable analysis.

CLINICAL-GENETIC ANALYSIS. Hardy-Weinberg equilibrium was assessed by the chi-square test. When possible, missing SNP calls were imputed via the expectation maximization algorithm (26). To assess the association of SNPs with study end points, each SNP was analyzed in a proportional hazards regression model that included the significant factors from the clinical multivariable analysis. In addition, haplotypes were determined for *ADRB1* and *ADRB2* using 2 coding SNPs in each gene. In our population, there were 3 *ADRB1* haplotypes (S49/R389, S49/G389, G49/R389) and 3 *ADRB2* haplotypes (R16Q27, G16E27, G16Q27) present. These 6 haplotypes were analyzed individually in the same manner as the individual SNPs (clinical-adjusted proportional hazards regression model).

In the primary analysis, SNPs or haplotypes were analyzed in the models with a 0/1/2 code reflecting the number of copies of the minor allele for a particular SNP. The expectation maximization algorithm was used to estimate the number of copies from 0 to 2 of each haplotype for each individual. Secondary analyses were also performed where the heterozygotes were combined either with the 0 copy (01/2; wild type or 1 copy of minor allele vs. 2 copies of minor allele) or with the 2 copy group (0/12; wild type vs. at least 1 copy of minor allele). In addition, the 5 SNPs were assessed in a combined model to evaluate whether there was an aggregate genetic effect. All analysis was performed using the R statistical package (27).

STUDY POWER. Given the cohort size, event rate, and range of gene allele frequencies analyzed, this study was 80% powered to detect between a 9% difference in survival (for most prevalent SNP) and 13% difference in survival (for least prevalent SNP).

Results

Clinical analysis. The study cohort consists of 637 subjects (CATHGEN n = 344, Registry of the Intermountain Heart Collaborative Study n = 293), whose complete baseline clinical characteristics are shown in Table 1. All 637 patients had LV systolic dysfunction and were discharged on a combination of β-blocker (metoprolol or carvedilol), ACEI or ARB, and loop diuretic; 69% had ischemic heart disease and 22% had implanted defibrillator devices.

There were 190 events (29.8%; 150 deaths, 40 transplants) over a median follow-up of 1,070 days (2.9 years; range 5 to 3,188 days). Minimum follow-up for a subject without an event was 248 days. Clinical factors selected for univariable end point analysis included those previously shown to be clinical predictors of survival in the Seattle HF model (age, gender, LVEF, NYHA functional class, HF etiology, systolic blood pressure, hemoglobin, and statin use) (28). In addition to these factors, we also studied the effect of race, history of diabetes, β-blocker medication, and presence of an implantable cardioverter-defibrillator (ICD) device on survival in our cohort. Eight clinical factors met the pre-defined univariable significance of $p < 0.1$ for inclusion in the multivariable model (Table 2). Of these, 4 retained significance ($p < 0.05$) in the multivariable analysis: age ($p = 0.006$), male gender ($p = 0.005$), low EF ($p = 0.0002$), and low hemoglobin ($p = 0.0001$). Systolic blood pressure showed a trend toward significance (Table 2).

Clinical-genetic analysis—single SNPs. Genotypes were generated for 637 patients with a call rate for all SNPs across the entire cohort of 98.3%. All alleles were in Hardy-Weinberg equilibrium, and minor allele frequencies for our cohort were in agreement with other major studies:

Table 1 Baseline Clinical Characteristics

Clinical Factor	Combined Cohort (n = 637)
Age (yrs)	61.7 ± 13.34
Men	471 (74)
Caucasian	481 (75)
Metoprolol	361 (56.7)
Carvedilol	276 (43.3)
EF (%)	27 ± 8.63
EF determined by ventriculogram	377 (59.2)
EF determined by echocardiogram	179 (28.1)
EF method not documented	81 (12.7)
NYHA functional class	
I	11 (1.7)
II	117 (18.4)
III	218 (34.2)
IV	112 (17.6)
Unknown	179 (28.1)
SBP (mm Hg)	134 ± 23
Hemoglobin (g/dl)	14 ± 1.88
Statin use	372 (58.4)
History of diabetes	189 (29.7)
History of hypertension	403 (63)
History of myocardial infarction	236 (37)
Ischemic	440 (69.1)
Nonischemic	197 (30.9)
Nonischemic "clean coronary" subgroup	138 (22)
Biventricular pacemaker defibrillator	39 (6)
Implanted defibrillator; includes patients with biventricular pacemaker defibrillator	141 (22.1)

Values are presented as n (%) or mean ± SD.
EF = ejection fraction; NYHA = New York Heart Association; SBP = systolic blood pressure.

ADRB1 G49 15%, G389 29.5%, and *ADRB2* R16 40%, E27 36.5% (12,21,29,30). Allele frequencies for the deletion polymorphism in *ADRA2C* differed by race, but were in Hardy-Weinberg equilibrium for each race when considered separately.

We found no significant effect on transplant-free survival for the primary analysis of 5 SNPs in the *ADRB1, ADRB2,* or *ADRA2C* genes (Fig. 1, Table 3). A death-only analysis also did not yield significant results. Considering the potential influence of ICDs on outcome, we performed secondary SNP analyses in the device (n = 141) and no-device (n = 496) subgroups, but did not identify a significant effect. The number of patients with biventricular ICDs was too small (n = 39) to provide any further meaningful analysis. Other independent secondary subgroup analyses of the "clean coronary" nonischemic patients and NYHA functional class III/IV patients were also noninformative.

A weak univariable trend toward better survival in black patients was observed, as an additive function of the number of alleles in the *ADRA2C* deletion polymorphism (hazard ratio [HR]: 0.55, 95% confidence interval [CI]: 0.28 to 1.11, p = 0.094 for black patients only; compared with HR: 0.95, 95% CI: 0.57 to 1.59, p = 0.85 for Caucasians only) (Figs. 1E and 1F). There were no other trends for Caucasian or black patients when performing secondary analyses within each race.

Clinical-genetic analysis—haplotypes. We analyzed 3 haplotypes for both *ADRB1* (S49/R389, S49/G389, G49/R389) and *ADRB2* (R16Q27, G16E27, G16Q27) that were inferred using the expectation maximization algorithm and a 0/1/2 coding to reflect the number of copies of each particular haplotype. We found no genetic association in any of the primary haplotype analyses or in any of the secondary subgroup analyses described above.

Discussion

Based on the potential of adrenergic receptor genetics to influence survival in HF patients, we chose to examine a cohort of clinically treated HF patients who had been prescribed metoprolol or carvedilol. To extend published studies in this area by White et al. (30), de Groote et al. (29), and Shin et al. (21), our cohort included a larger number of patients from 2 centers and a greater proportion of nonwhite patients, and we comprehensively examined SNPs and haplotypes in 3 major adrenergic receptor genes (Tables 4 and 5). The cohort was enrolled from patients who underwent cardiac catheterization between January 1, 1998, and June 30, 2006, which represents an interval of standardized HF pharmacotherapy. Subjects were included who met the criteria of LV systolic dysfunction (EF ≤40%), had a clinical diagnosis of HF, were more than 30 days from previous myocardial infarction at the time of catheteriza-

Table 2 Clinical Analysis

Variable	HR	95% CI	p Value
Univariable analysis			
Age at baseline	1.020	(1.008–1.032)	0.0007*
Male gender	1.391	(0.981–1.972)	0.064*
Baseline EF	0.975	(0.959–0.991)	0.003*
Hemoglobin	0.882	(0.818–0.950)	0.001*
Systolic blood pressure	0.992	(0.985–0.999)	0.026*
Ischemic etiology	1.700	(1.210–2.380)	0.0021*
ICD	1.600	(1.150–2.230)	0.005*
Black race	0.508	(0.323–0.801)	0.004*
NYHA functional class	1.204	(0.955–1.519)	0.12
Statins	0.903	(0.679–1.202)	0.48
Diabetes	1.069	(0.788–1.450)	0.67
β-blocker type	0.828	(0.622–1.102)	0.19
Multivariable clinical model			
Age at baseline	1.017	(1.004–1.031)	0.01300†
Male gender	1.711	(1.126–2.600)	0.01200†
Baseline EF	0.963	(0.945–0.982)	0.00011†
Hemoglobin	0.852	(0.783–0.927)	0.00021†
Systolic blood pressure	0.993	(0.985–1.000)	0.05800
Ischemic etiology	1.318	(0.894–1.943)	0.16000
ICD	1.390	(0.970–1.990)	0.074
Black race	0.673	(0.406–1.116)	0.12000

*Factors with p < 0.10 in univariable analysis were included in multivariable model. †Significant factors (p < 0.05) for transplant-free survival.
CI = confidence interval; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; other abbreviations as in Table 1.

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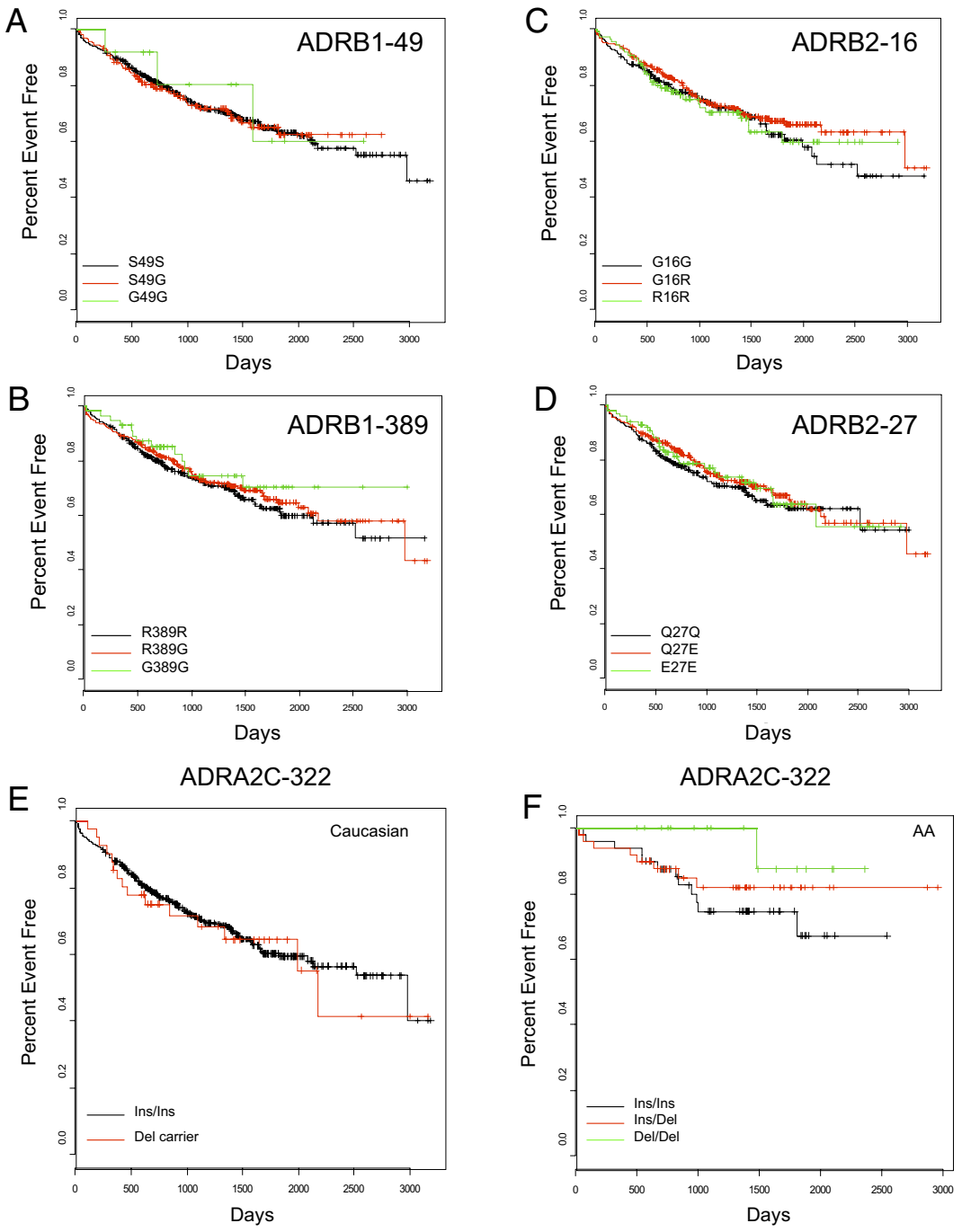

Figure 1 **Kaplan-Meier Survival Curves**

Kaplan-Meier curves showing the percent transplant-free survival for subjects over time (in days) for single-nucleotide polymorphisms tested. **(A)** *ADRB1*-49. **(B)** *ADRB1*-389. **(C)** *ADRB2*-16. **(D)** *ADRB2*-27. **(E)** *ADRA2C*-del322-325 (Caucasian). **(F)** *ADRA2C*-del322-325 (African American). **Black line** = homozygous major allele (0 copies minor allele); **red line** = heterozygous (1 copy minor allele); **green line** = homozygous minor allele (2 copies minor allele). **Vertical tick marks on the curves** represent censored subjects.

tion, and were discharged on standard HF medications including β-blocker, ACEI or ARB, and/or loop diuretic. Patients were followed up to the end point of death or transplant.

In this study, older age, male gender, low EF, and low hemoglobin at baseline negatively influenced survival. This is consistent with what would be expected from other predictive models such as the Seattle HF score, and also

Table 3 Clinical-Genetic Analysis

	HR	95% CI	p Value
SNP			
ADRB1 G49	1.120	(0.822–1.525)	0.470
ADRB1 G389	0.980	(0.773–1.242)	0.870
ADRB2 R16	1.040	(0.835–1.294)	0.730
ADRB2 E27	0.888	(0.710–1.110)	0.300
ADRA2C del Caucasian	0.951	(0.570–1.586)	0.850
ADRA2C del African American	0.553	(0.276–1.107)	0.094
Haplotype			
ADRB1 GR	1.120	(0.822–1.525)	0.470
ADRB1 SR	0.962	(0.771–1.201)	0.730
ADRB1 SG	0.980	(0.773–1.242)	0.870
ADRB2 RQ	1.040	(0.835–1.294)	0.730
ADRB2 GQ	1.115	(0.863–1.440)	0.410
ADRB2 GE	0.888	(0.710–1.110)	0.300

Abbreviations as in Table 2.

reiterates the importance of recognizing anemia in this condition (28,31). At the same time, we found no significant effect of the polymorphisms or haplotypes we analyzed in *ADRB1, ADRB2,* or *ADRA2C* on transplant-free survival. Despite showing almost identical haplotype frequencies, we did not replicate either an adverse effect on transplant-free survival of 2 copies of the *ADRB2* RQ haplotypes previously reported by Shin et al. (21), or an adverse effect of 2 copies of the *ADRB2* GQ haplotype as previously reported by de Groote et al. (30) (Table 4). This may be in part attributable to smaller numbers of patients in those studies or to a population effect. In terms of the other SNPs analyzed, the published datasets show no effect of the *ADRB1* R389G SNP in HF survival in now over 1,500 β-blocker–treated subjects (637 from this study) (Table 6). Furthermore, no effect of SNPs in *ADRB1* (S49G), *ADRB2* (G16R and Q27E), or haplotypes in *ADRB1* have been found in over 1,200 β-blocker–treated subjects. Taken together, these results lead us to conclude that there is no significant association between adrenergic receptor genotype and survival in the clinical setting of HF treatment with metoprolol and carvedilol.

For the *ADRB1* R389G polymorphism, a recent BEST DNA substudy of 1,040 patients (515 treated) has shown a significant pharmacogenetic association in HF survival between bucindolol-treated R389 homozygotes and placebo (HR: 0.62, 95% CI: 0.40 to 0.96, p = 0.03) (16). Bucindolol has a specific pharmacologic profile (reviewed by Liggett et al. [16]), which may be the basis for the unique association of *ADRB1* R389R with treatment response in heart failure. Unlike metoprolol (but like carvedilol), bucindolol has affinity for both the β_1- and β_2-AR subtypes. Although initial studies in nonhuman tissue suggested a partial agonist effect in the heart, subsequent studies in humans showed no such effect. In ex vivo human trabeculae studies from failing explanted hearts, bucindolol showed inverse agonist properties (i.e., it decreased contractility), but only in *ADRB1* R389 homozygotes (16). In contrast, carvedilol had no such effect (16), nor does metoprolol (S.B. Liggett, unpublished data, June 2007). In addition, bucindolol evokes a distinct sympatholysis effect (by an unclear mechanism), lowering plasma norepinephrine levels to a much greater extent than metoprolol or carvedilol. Taken together, these characteristics of bucindolol may account for the pharmacogenetic effect of *ADRB1*-389 when this drug is used for heart failure treatment. Another possibility is that a BEST-specific population effect exists; however, this can only be addressed through independent replication.

Study limitations. Lacking a placebo-controlled, single β-blocker trial such as the genetic substudies performed in BEST and MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure), we used intent to treat with β-blockers at discharge as an inclusion criterion. To address this limitation, we evaluated medication records for 310 patients at a second time point at least 60 days from the index date, and found that 94% remained on β-blocker therapy. Sufficient data did not exist to perform a genotype–β-blocker dosage effect in this study. We identified HF patients in cardiac catheterization

Table 4 Haplotype Frequencies and Copy Numbers for *ADRB1* and *ADRB2*

	ADRB1 SR	*ADRB1* SG	*ADRB1* GR	*ADRB2* GQ	*ADRB2* GE	*ADRB2* RQ
0 copies						
Current cohort	122 (19%)	320 (50%)	462 (73%)	376 (59%)	263 (41%)	239 (38%)
Shin et al. (21)	52 (23%)	93 (41%)	174 (77%)	135 (59%)	98 (44%)	85 (37%)
de Groote et al. (29)	—	—	—	—	—	—
1 copy						
Current cohort	316 (50%)	259 (41%)	161 (25%)	229 (36%)	277 (44%)	290 (46%)
Shin et al. (21)	112 (49%)	108 (48%)	53 (23%)	76 (33%)	99 (43%)	104 (46%)
de Groote et al. (29)	—	—	—	—	—	—
2 copies						
Current cohort	197 (31%)	56 (9%)	12 (2%)	31 (5%)	96 (15%)	107 (17%)
Shin et al. (21)	63 (28%)	26 (11%)	0 (0%)	16 (7%)	30 (13%)	38* (17%)
de Groote et al. (29)	—	—	—	44† (10%)	82 (18%)	61 (14%)

*Associated with unfavorable outcome by Shin et al. (21). †Associated with unfavorable outcome by de Groote et al. (29).

Table 5 Clinical Factors in Heart Failure Survival Studies Studying Adrenergic Receptor Genetics

Clinical Factor	Current Cohort	Shin et al. (21)	de Groote et al. (29)	White et al. (30)
Study number	637	227	444	600 (307 treated)
Primary end point	Death + transplant	Death + transplant	Cardiac death or urgent transplant	All-cause mortality or hospitalization
Age (yrs)	61.7 ± 13.34	54.9 ± 13	56.6 ± 11.9	66.2 ± 8.7
Men	471 (74)	156 (68)	364 (82)	507 (84.5)
Caucasian	481 (75)	188 (82)	444 (100)	584 (97.3)
Metoprolol	361 (56.7)	NA	0	307 (51.1)
Carvedilol	276 (43.3)	NA	NA	0
Bisoprolol	0	0	NA	0
β-blocker, unspecified	0	183 (81%)	444 (100)	0
EF (%)	27 ± 8.63	25 ± 12	32 ± 12	30 ± 10
NYHA functional class	—	—	—	—
I	11 (1.7)	14 (7)	—	0
II	117 (18.4)	85 (27)	—	267 (44.5)
III	218 (34.2)	98 (43)	III + IV (25)	312 (52)
IV	112 (17.6)	30 (13)	—	21 (3.5)
Unknown	179 (28.1)	—	—	—
History of diabetes	189 (29.7)	56 (25)	134 (30)	95 (15.9)
Ischemic	440 (69.1)	105 (46)	191 (43)	424 (70.6)
History of MI	236 (37)	101 (45)	—	308 (51.3)
History of HTN	403 (63)	120 (53)	173 (39)	200 (33.3)

Values are presented as n (%) or mean ± SD.
HTN = hypertension; MI = myocardial infarction; NA = not available; other abbreviations as in Table 1.

laboratory-based registries as opposed to HF clinics, and although the baseline clinical characteristics are remarkably similar to those of other studies (Table 5), we cannot exclude other potential biases of this approach. The inherent difficulty in defining the onset of HF in an individual patient remains an overall limitation for a time-to-event analysis. For consistency across patients and sites in this study, we defined the date of catheterization as the index time. Finally, although we examined the most common coding SNPs in *ADRA2C*, *ADRB1*, and *ADRB2*, we cannot exclude that other SNPs in noncoding regions or more extensive haplotypes not tested in this study may be associated with β-blocker response in heart failure (25,32,33).

Conclusions

We conclude that the findings of the current study and the weight of published evidence show no effect of the selected β_1-, β_2-, and α_{2C}-AR polymorphisms or limited haplotypes on survival in HF patients treated with metoprolol or carvedilol. The complexities of HF and varied responses to HF polypharmacy (some of which

Table 6 Results of Genetic Studies in β-blocker–Treated Heart Failure Patients With Survival End Points

	ADRB1 S49G	*ADRB1* R389G	*ADRB2* G16R	*ADRB2* Q27E	*ADRA2C* Del322-325	*ADRB1* 49/389 SR, SG, GR	*ADRB2* 16/27 RQ, GE, GQ
Current cohort	p = 0.47	p = 0.87	p = 0.73	p = 0.30	p = 0.85 Caucasian, p = 0.094 African American	NS	NS
Shin et al. (21)	NS	NS	NS	NS	NS	NS	2 copies RQ HR: 1.91, 95% CI: 1.09 to 3.36 (p = 0.024)
de Groote et al. (29)	NS	NS	NS	NS	—	NS	2 copies GQ p = 0.01 (univariate)
White et al. (30), MERIT-HF	—	p = 0.74	—	—	—	—	—
Liggett et al. (16), BEST	—	R389R bucindolol-treated patients had better survival compared with R389R placebo-treated patients HR: 0.62, 95% CI: 0.40 to 0.96 (p = 0.03)	—	—	Unpublished	—	—

NS = not statistically significant; other abbreviations as in Table 2.

have a genetic origin) warrant future prospective studies to dissect the impact of multiple genes and pathways on treatment response in HF.

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Key Words: heart failure ■ genetics ■ adrenergic receptors ■ β-blockers ■ haplotypes.

APPENDIX

For primer and probe sequences, please see the online version of this article.